OUTLINE OF THE PROPOSED WORK FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN PHARMACEUTICAL SCIENCES

A SYNOPSIS

"Synthesis and Biological evaluation of some novel derivatives of 2 Azetidinone"

Submitted for the consideration of

Registration for the Degree of *Doctor of Philosophy*

In the Faculty of Pharmaceutical Sciences and Technology,

By

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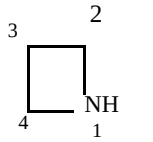
1. Abstract:

Most of the present diseases are due to the invasion by many pathogenic micro-organisms like bacteria and fungi. To treat this disease many potent and broad spectrum antibiotics were discovered, but these are accompanied by side effects.

Azetidinone derivatives are widely distributed in nature and they have been reported to possess very interesting pharmacological activity like antibacterial activity etc. when one biologically active molecule is linked to another, the resultant molecule generally has increased potency. In the present work we plan to synthesize azetidinone moiety

2. Introduction:

Azetidin (a), 1-azetin (b), 2-azetin (c) and azete (d) are the nitrogen analogues of cyclobutene and cyclobutadiene respectiveily. Azetidins are well studied, in particular their derivatives the azetidin -2- ones (β-lactums) have received considerable attention mainly because of the antibacterial properties of penicillin and cephalosporines. The chemistry of both 1-and 2-azetidins has been developed only since the mid-1960 and these systems have not yet been comprehensively reviewed.

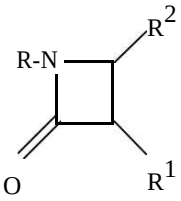


(a)

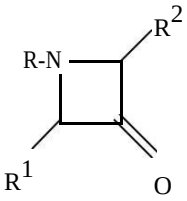
(b)

(c)

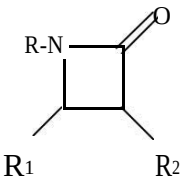
(d)



Azetidin-2-one



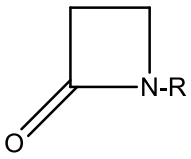
Azetidin-3-one



Azetidin-4-one

Structure

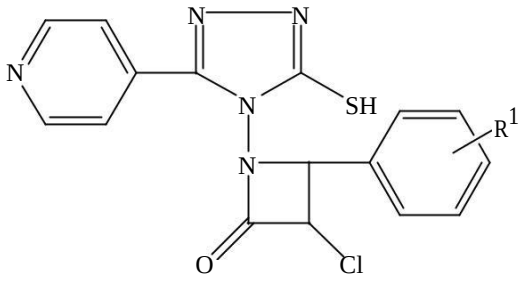
2-azetidinone (1) is a hydrolytically sensitive colourless solid, having melting point 73-74°C. Other simple azetidin-2-ones are usually low melting solids or oils.[1]



(1)

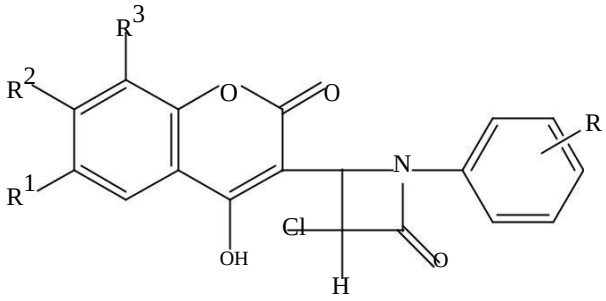
Azetidin-2-ones as antibacterial agents:

R. Priyadarsini et al[2] have prepared azetidinones and evaluated them for antibacterial activity.



R^1=2-Cl, 3-OCH_3

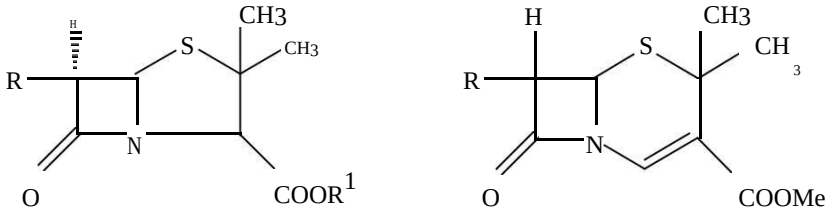
V.V. Mulwad et al[3] reported the synthesis and antimicrobial property of cetain 4-hydroxycoumarin azetidinones.



$R^1=R^2=R^3$=H

R=4-NO_2

Myer et al[4] synthesized the following azetidin-2-ones and noted their antibacterial action.



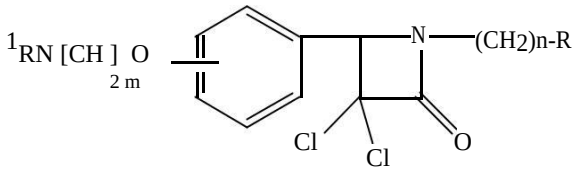
R = H, Ph-CH_2, t-Butyl, -OMe

R^1 = OH

2-Azetidinones as anti-inflammatory drugs:

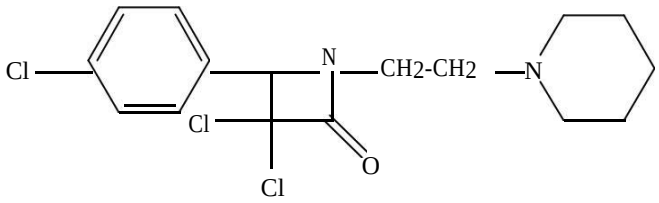
Piffer et al[5] synthesized large number of 2-Azetidinones and evaluated them for anti inflammatory action.

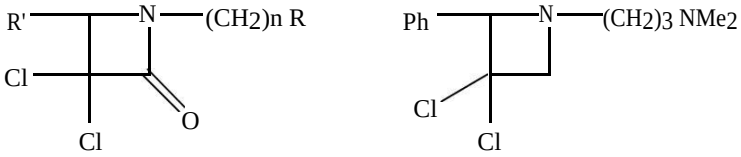
Azetidinones of the following type has been synthesized and they showed anti-inflammatory activity.



m=2-5, n=0-4
r= alkyl, cycloalkyl
R^1=heteroalkyl

The compounds listed below showed anti-inflammatory property proving their usefulness as anti-inflammatory agents.

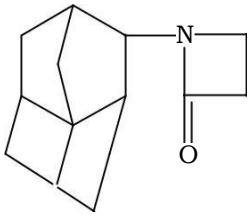




n = 0-2
R = dialkyl amines heteroamines
R' = aryl

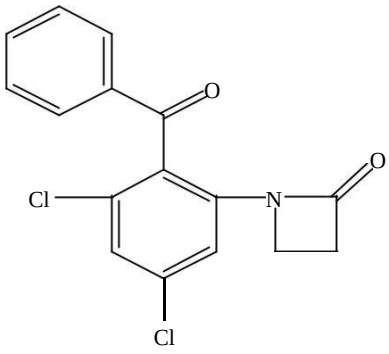
2-Azetidinones as effective antiviral drugs:

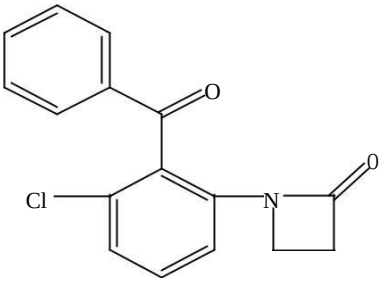
Levinine et al[6] synthesized certain 2- Azetidinones and carried out their antiviral activity.

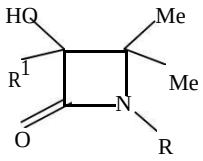


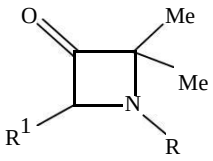
2-Azetidinones as hypotensive drugs:

Several 2-Azetidinones and 3-Azetidinones have been prepared and Screened against hypotensive property







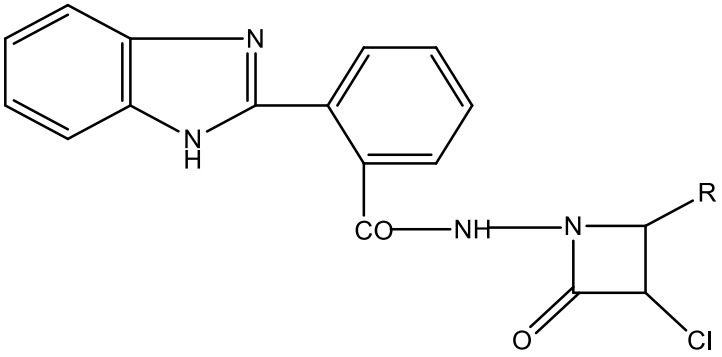


R=H, CH_3, C_2H_5, $C(CH_3)_3$

R^1=H, Ph

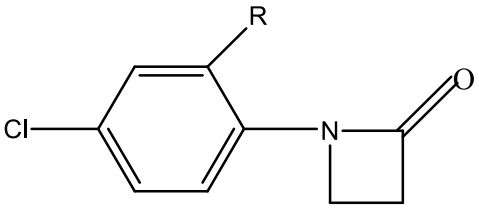
2-Azetidinones as an antitubercular agent:

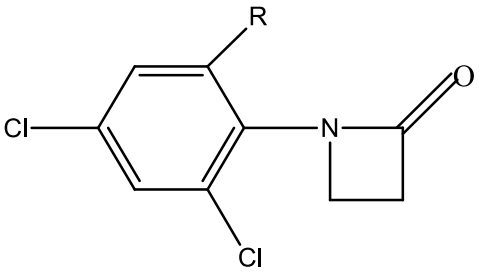
H. H. Parekh et al[7] have synthesized 4-aryl -3- chloro -1- (Benzimidazole-2 yl-benzamido) -2- azetidinones and screened for antitubercular activity



2-Azetidinones as an anticonvulsant agent:

Wei et al[8] synthesized a number of azetidinones and tested them for anticonvulsant activity against electroshock and metrazole induced convulsions.





3. Literature Review:

A significant amount of data collected in a literature survey which high lighten the various methods for synthesis of azetidinone derivatives. The survey also revels azetidinone derivatives are able to show good pharmacological activity.

1. **Suresh P. et al (2016)**

   The present study shows Synthesis, characterization of 4-(furan-2-yl)-6-methyl-2-oxo-N-(3-chloro-4-oxo-2-arylazetidin-1-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide. All the synthesized novel compounds studied for antibacterial, antifungal activity.

2. **Dr. Subin M. Zachariah et al (2015)**

   The present study shows the various diverse biological activities such as anti-microbial anti-bacterial anti-convulsant, anti-tubercular and anti-inflammatory properties of 2-azetidinones derivatives.

3. **Darpan B. Patel et al (2017)**

   The present study reported novel approach for the synthesis of 3-chloro-4-phenyl-1-((s)-pyrrolidine-2-carbonyl) azetidine-2-one derivatives. These synthesized compounds screened for biological activity against different strains for their antibacterial and antifungal activity.

4. **A. Rajasekaran et al (2010)**

   The present study shows synthesis of, characterization and biological activity of some novel azetidinone as antitubercular, antibacterial, antifungal and anti-inflammatory.

5. **Snehal Lokhandwala et al (2013)**

   The present study shows synthesis of 3-chloro-1-(10-hydroxy-10-oxo-5,10-dihydro-phenophosphazin-2-yl)-4-(substituted phenyl)-azetidin-2-one. The lead compounds tested for antimicrobial studies and showed significant activity at low and high concentration as compared to standard.

6. **Sibaji Sarkar et al (2017)**

   The present study shows synthesis, characterization and antimycobacterial activity of some benzothiazole containing azetidinones derivatives.

7. **Reshma Kayarmar et al (2017):**

   The present study shows synthesis and characterization of novel imidazoquinoline based 2-azetidinones as potent antibacterial, antifungal and anticancer activity.

8. **Karthikeyan Elumalai et al ((2013)**

   The present study shows Design, synthesis biological evaluation such as antimicrobial and antimycobacterial activity of some novel isoniazide cyclocondensed azetidinones.

4. Aim and Objective:

Aim:

The present study aims to synthesize and biological evaluation of some novel derivatives of 2 Azitidinone.

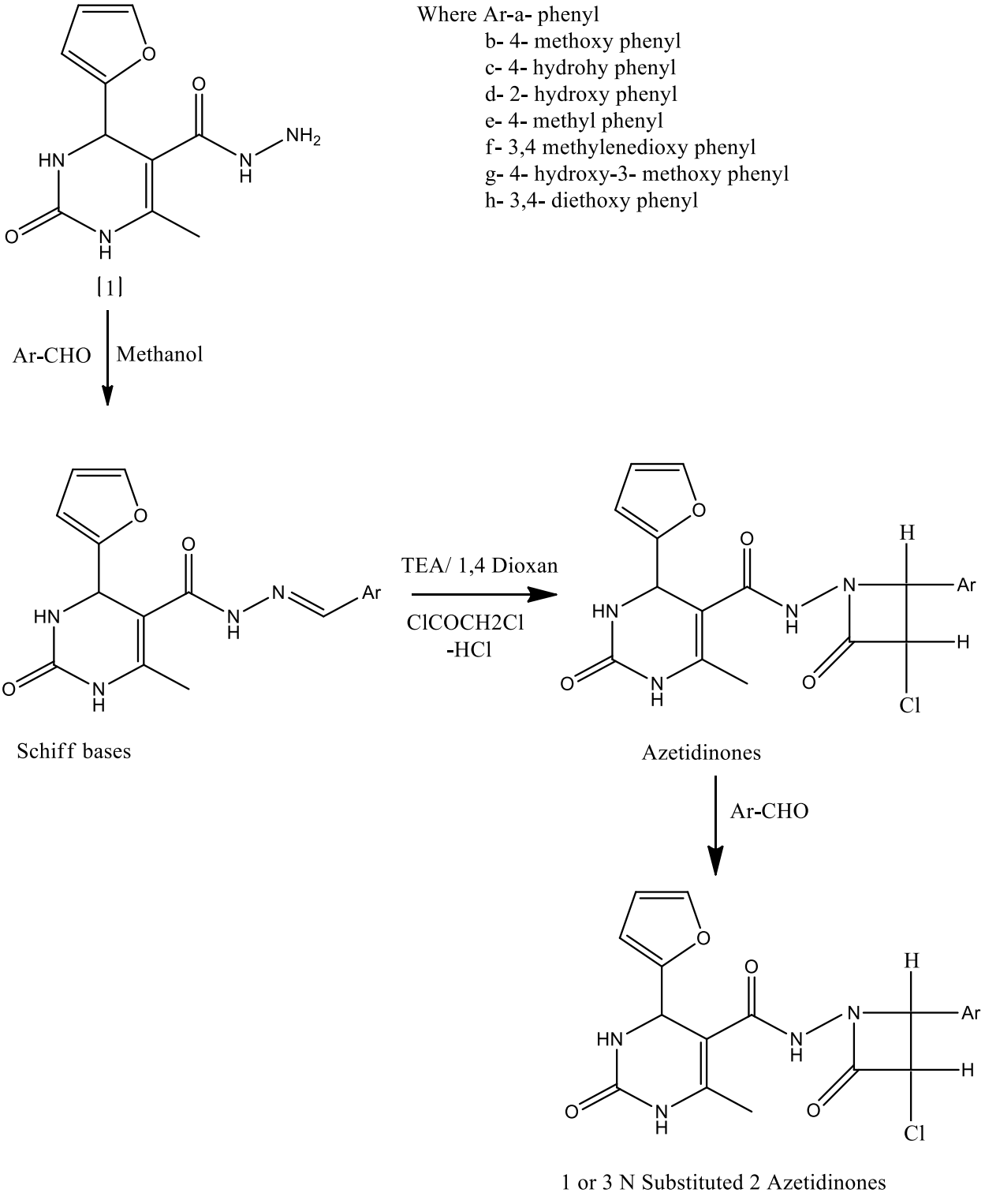
Objectives:

The present work is undertaken with the following objectives.

1. To synthesize novel derivatives of 2-azetidinone.
2. To establish the structure of synthesized compounds based on chemical and spectral data.
3. To carry out pharmacological screening of synthesized compounds.

5. Methodology to be adopted:

A) Proposed synthetic pathway.



Step I: Synthesis of Schiffs bases.

A mixture of 4-(furan-2-yl)-6- methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbo hydrazide refluxed with aromatic aldehyde in ethanol to yield corresponding schiffs bases.

Step II: Synthesis of 2-Azetidinones.

The above synthesized schiffs bases and triethyl amine dissolved in 1,4-dioxan and chloroacetyl chloride add slowly as a result to give desire 2-azetidinones.

Step III: Synthesis of 2-Azetidinones derivatives.

The synthesized substituted 2-azetidinones and triethyl amine dissolved in 1,4-dioxan and chloroacetyl chloride add slowly to yield product of 1or 3 N substitued 2-azetidinones derivatives.

B) Characterization of synthesized compounds:

By Chromatographic and Spectroscopic techniques

Chemicals and other reagents will be collected from standard companies. The compound will be synthesized; the product will be purified by chromatographic technique column chromatography, preparative chromatography.

The chemical structure of the synthesized compounds would be established on the basis of physical, chemical and analytical data, melting point of synthesized compound is determined in open capillary tube and is uncorrected.

The selected synthesized compounds will be characterized by IR, NMR, 13CNMR and Mass spectral data. This will be collected by sending the sample to other advanced research centers like NCL,Pune.

C) Biological Evaluation:

a) Antimicrobial activity:

Antibacterial activity will be carried out by disc-diffusion method, using *Bacillus subtilis, bacillus pumilis, Escherichia coli,* and *Psedomonous aeruginosa* organism.

b) Anti fungal activity: Anti fungal activity will be carried out by using potato dextrose agar medium against *Aspergillus niger* and *Candida albicans* organisms.

c) Antitubercular activity:

Antitubercular activity will be carried out against mycobacteria.

d) Anticonvulsant activity:

Anticonvulsant activity will be carried out by using Swiss albino mice.

D) Source of data:

The data of present literature and further investigation will be carried out by referring different Heterocyclic book, Chemical abstract, National and International journals like Indian journal of heterocyclic chemistry, European journal of Medicinal chemistry and Bioorganic and Medicinal chemistry letters on synthetic procedure and by depending on pharmacological activity.

6. Importance of study /society application:

2-Azetidinone showed a broad-spectrum of activity on various pathogens and a considerable research has been done on the synthesis of new potent antibacterial and antifungal 2-azetidinones. β-Lactams really are evergreen bioactive molecules and are still the most prescribed antibiotics used in medicine. These are considered as an important contribution of science to humanity. Azetidinone is an important heterocyclic nucleus and has gained wide acceptance across the world but bacteria continue to challenge the society and scientific community with their mortality.

2-Azetidinone is very important pharamacophore in medicinal chemistry. Further molecular modeling may give better pharamacophore. So the present study aims to focus on important chemical moiety that is azetidinone and their derivatives which can facilitate new potent antibacterial and antifungal agent.

7. Proposed work plan:

Sr. no	Activity	Months
1.	Literature survey	03
2.	Selection and Procurement of drug	03
3.	Synthesis of new compounds	15
4.	Purification and Characterization of new synthesized compounds	03
5.	Biological evaluation of synthesized Compounds	03
6.	Communication with Research Journals	03
7.	Completion of research work and submission of report	06
	Total	36

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